REMARKS

This paper is being filed in response to the Office Action dated December 4, 2002 for the above-referenced patent application.

Claims 1-34, 41-59 and 63-65 are pending. Claims 35-40, 60-62, 66 and 67 have been cancelled. Claims 1-7, 9, 11, 12, 15, 26, 41-44, 46, 47, and 49 have been amended to correct informalities, as recommended by the Examiner. Support for the amendments to claims 1, 7, 15, 30, 41, 43, 49, and 63 is found at page 14, para 0014 and in Example 7 (pp. 34-35). Support for all other amendments can be found in the specification and claims as originally filed. No new matter has been added by the amended claims.

Pursuant to the Revised Amendment practice announced in the Pre-OG Notices dated Jan. 31, 2003, applicants present the "Amendments to the Claims," and Remarks" sections each on a separate sheet and submit only one version (with markings) of amendments made to the claims in a complete listing of all claims in ascending order with status identifiers.

CLAIM OBJECTION

The Examiner has objected to Claim 26 under 37 C.F.R. § 1.75(c) as being in improper format because a multiple dependent claim should refer to claims in the alternative.

In response, Claim 26 has been amended accordingly. Applicants request that the Examiner review and examine Claim 26 on its merits.

THE REJECTION UNDER 35 U.S.C. § 101 SHOULD BE WITHDRAWN

Claims 1-14 and 41-48 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. The Examiner alleges that the claims drawn to "tolerogenic dendritic cell" read upon a naturally occurring dendritic cell, which is a product of nature and unpatentable. The Examiner has suggested that the claims be amended to recite an "isolated" dendritic cell. Claims 1-7, 9, 11, 12, 15, 41-44, 46, 47, and 49 have been amended to reflect the Examiner's recommendation. Thus, Applicants respectfully request that the rejection of claims 1-14 and 41-48 under 35 U.S.C. § 101 be withdrawn.

THE REJECTION UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

Claims 1-25, 27-34, 41-59 and 63-65 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Storm et al. (US 2002/0164311 A1) in further view of Thomson et al. (US 5,871,728), Lu et al.$_1$ (Journal of Leukocyte Biology), Lu et al.$_2$ (Gene Therapy), and Bielinska et al.

The Examiner alleges that Storm et al. teach methods of inhibiting rejection of a transplanted tissue in a mammal and inhibition of autoimmune related tissue destruction by introducing into a cell DNA comprising at least one regulatory element including a synthetic regulatory DNA sequence from at least one of NF-κB, NF-IL-6, IL-6, LRE, AP-1, p91/stat, or the IL-6 response elements. Because Storm et al. allegedly teach a tolerogenic dendritic cell comprising an oligonucleotide having one or more NF-κB binding sites inhibiting autoimmune

related tissue destruction in a mammal, the Examiner contends that it would have been obvious to one of ordinary skill in the art to make a tolerogenic dendritic cell comprising an oligonucleotide having one or more NF-κB binding sites.

In addition, the Examiner alleges that Bielinska et al. teach regulation of gene expression with double-stranded phosphorothioate oligonucleotides of NF-κB. In addition, the Examiner alleges that Bielinska et al. teach an oligodeoxyribonucleotide identical to that of SEQ ID NO:1 of the present invention. Because Bielinska et al. teach that an oligonucleotide having one or more NF-κB binding sites regulate gene expression, the Examiner contends that one of ordinary skill in the art would have expected success in making a tolerogenic dendritic cell comprising an oligonucleotide having one or more NF-κB binding sites. Furthermore, the Examiner contends that it would have been obvious to one of ordinary skill in the art to devise a method for enhancing tolerogenicity in a mammal given the teachings of Storm et al. and Bielinska et al.

The Examiner alleges that Thomson et al. teach enhancing tolerogenicity in a mammal host comprising propagating immature dendritic cells from a mammalian donor, culturing the dendritic cells and administering the dendritic cells to the host, as well as incubation of the dendritic cells in the presence of cytokines. Because Thompson et al. teach such methods to effect dendritic cell maturation and enhance the immune response of a host mammal, the Examiner alleges that one of ordinary skill in the art would have been motivated to propagate immature dendritic cells from a mammalian donor, culture the dendritic cells and administer the tolerogenic cells to a host. The Examiner also alleges that one would have been motivated and

expected success in producing tolerogenic dendritic cells by incubation in the presence of one or more cytokines and pharmaceuticals, since this has been taught in the prior art.

Applicants respectfully traverse the Examiner's rejections. To establish *prima facie* case of obviousness, three basic criteria must be met (MPEP 2142). First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify the reference or to combine the teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1981).

The present invention

The present invention relates to a tolerogenic dendritic cell comprising a oligodeoxyribonucleotide having one or more NF-κB binding sites, wherein the binding sites inhibit NF-κB transcriptional activity. The oligodeoxyribonucleotide, taken up by the dendritic cells, functions to inhibit NF-κB's activity as a transcription factor by binding to NF-κB binding sites to prevent its association with DNA. As a result, the tolerogenic dendritic cell having the oligodeoxyribonucleotide inhibits NF-κB's activity by mediating induction of dendritic cell activation and maturation. The oligodeoxyribonucleotide of the present invention does not encode a functional protein.

The present invention further relates to methods of producing and using the dendritic cell for enhancing tolerogenicity in a mammalian host. The methods comprise (a) propagating immature isolated dendritic cells from a mammalian donor, (b) incubating the isolated dendritic cells with an oligodeoxyribonucleotide having at least one NF-κB binding site under conditions wherein the dendritic cells internalize the oligodeoxyribonucleotide (c) culturing the isolated dendritic cells, and (d) administering the isolated tolerogenic dendritic cells to said host.

Cited art

In contrast to the present invention, Storm et al. teach a cell comprising a DNA molecule which encodes a functional protein, *e.g.* IL-10, TGF-β, IL2 suppression factors, etc., to suppress the immune response and prevent graft rejection. Storm et al. disclose methods of localized immunosuppression by expression and secretion of various immunosuppressive proteins in cells that may be transplanted into a mammal. Storm et al. teach the incorporation of NF-κB binding sites as promoter elements regulating the expression of the immunosuppressive protein of interest (p.11, para 0079). NF-κB is expressed and fully functional as a transcription factor to promote gene expression of an immunosuppressive protein of interest. Claim 1, as amended, recites the limitation, "wherein the NF-κB binding sites inhibit NF-κB transcriptional activity." There is no teaching in Storm et al. of a tolerogenic dendritic cell comprising a DNA molecule that comprises one or more NF-κB binding sites, *i.e.* having the capacity to bind to and inhibit NF-κB transcriptional activity.

In fact, Storm et al. teaches away from the present invention. Because Storm et al. propose expression of a functional NF-κβ to mediate expression of an immunosuppressive protein, it directly conflicts with the rationale for the present invention. The introduction of an oligodeoxyribonucleotide having NFκB binding in the present invention functions to inhibit NFκB transcriptional activity.

In order for the present invention to be obvious over Storm et al., there must be some suggestion to inhibit the activity of NF-κβ to mediate immunosuppression as disclosed by the present invention. Because Storm et al. provides no motivation or suggestion to inhibit NFκB activity, one of skill in the art would not look to Bielinska et al. for guidance. Bielinska et al. disclose double stranded phosphorothioate oligonucleotides containing consensus sequences that bind to NF-κB to inhibit its activity. Since there is no suggestion to combine the references, there would be no reasonable expectation of success.

Storm et al. also do not teach a method of enhancing tolerogenicity in a mammalian host by (a) propagating immature isolated dendritic cells from a mammalian donor, (b) incubating the isolated dendritic cells with an oligodeoxyribonucleotide comprising at least one NFkB binding site and having at least one NF-κB binding site under conditions wherein the dendritic cells internalize the oligodeoxyribonucleotide and the NF-κB binding sites inhibit NF-κB transcriptional activity (c) culturing the isolated dendritic cells, and (d) administering the isolated tolerogenic dendritic cells to said host. Although Thompson et al. teach steps (a), (c) and (d), it fails to teach step (b) of the present invention. As discussed above, Storm et al. provides no motivation or suggestion to combine the disclosure of Bielinska et al. and Thompson

et al. Thus, one of skill in the art would not have a reasonable expectation of success. Furthermore, there is no combination of the above-cited references which can provide a teaching of each and every element of the claimed invention to render the invention obvious.

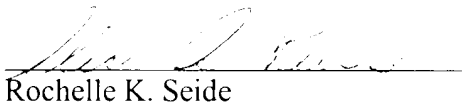
Applicants respectfully request that the rejection of Claims 1-25, 27-34, 41-59 and 63-65 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

For all the foregoing reasons, Applicants respectfully request allowance of the pending Claims 1-34, 41-59 and 63-65 and the issuance of a timely Notice of Allowance. Applicants request a three month extension of time and enclose herewith the required fee pursuant to 37 C.F.R. § 1.17(a)(3).

The Commissioner is hereby authorized to charge payment of any additional fees associated with this communication to Deposit Account No. 02-4377. Duplicate copies of this page are enclosed.

Respectfully submitted,



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